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THE ALBINO SERIES OF ALLELOMORPHS IN GUINEA-PIGS

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Albinism is one of the most familiar color conditions found in mammals. In all cases it has proved to be a simple Mendelian recessive to the pigmented condition. This was demonstrated for guinea-pigs by Castle and Allen in 1903. In the present paper evidence will be presented showing that in guinea-pigs there are two grades of pigmentation, intermediate between full intensity and albinism, which form with these a series of four allelomorphs with dominance in the order of increasing pigmentation.

The most highly pigmented condition is also the most familiar. To this condition, which we may call intensity, belong those types of guinea-pigs which show in the fur intense black pigmentation or the intense orange-yellow known as "red," or both. Examples are the blacks, the reds, the golden agoutis and the black-and-red tortoise-shells of the fanciers. All of these have black eyes.

The second condition in intensity and order of dominance contains color varieties which have long been known. In these black is reduced to a sepia-brown color much like human brown hair, known very inappropriately as "blue." Red is reduced to yellow or cream. The eye color remains black. Thus we have blues, creams, silver agoutis and blue-and-cream tortoise-shells in place of the four types mentioned as of the intense condition. That these four so-called dilute types, as well as others not mentioned, differ from the intense types by the same factor or factors has long been known. It is shown by the fact that one can start with any of these and by crosses with the appropriate intense variety produce any other dilute variety in the second generation at latest. The writer has done this for all of the types mentioned by starting with the cream variety.

The third condition is not so familiar as the others. It has appeared at the Bussey Institution only in the descendants of three guinea-pigs brought from Peru by Professor Castle in 1911. Among these black is reduced to sepia (or "blue"), indistinguishable from the "blue" of the dilutes. Red is reduced to white. Not a trace of yellow pigment has been found in guinea-pigs with this allelomorph. One of the most striking features of this condition is the glowing red color of the eyes, easily distinguishable from the black eyes of the intense and dilute guinea-pigs as well as from the pink eyes of the albinos. There is a deficiency of pigment in both retina and iris. Because of this feature this condition will be known as red-eye. It was announced as an allelomorph of albinism by Castle (1914). Permission has very kindly been given the writer to present in this paper data on the red-eye condition, in the work on which he has been associated. With the red-eye factor, the blacks, reds, golden agoutis and black-and-red tortoise-shells become red-eyed blues, red-eyed whites, red-eyed silver agoutis and red-eyed blue-and-white tortoise-shells, respectively. These four varieties have all been obtained by crossing one of them, the red-eyed silver agouti, with various stock guinea-pigs and extracting the different combinations in F_2. The red-eyed white is an interesting variety thus derived. Red-eyed whites have been tested by crosses with reds and creams and have been shown conclusively to be the red-eyed representative of these varieties, such crosses having given 9 reds, 3 creams, 6 red-eyed whites and 6 albinos only. This red-eyed white demonstrates most forcibly the complete inhibition of yellow in the presence of the red-eye factor.

In the albino condition black disappears from the coat except in patches on the nose, ears and feet, and occasionally some sootiness on the back. In this connection it is interesting to note that nose, ears and feet are generally the most highly pigmented regions in the dilute and red-eye conditions. In the albinos, yellow disappears entirely, just as in the red-eyes. The eyes are pink, due to the loss of all pigment from the iris and retina. The blacks and golden agoutis are replaced by sooty albinos; the reds, by clear albinos; and the black-and-red tortoiseshells, by albinos in which nose, feet and ears are sooty or white, depending on the location of the spots.

The effects of the four allelomorphs on the appearance of eye and fur may be tabulated as follows:

Effects of	On Eye Color	On Black Fur	On Yellow Fur
Intensity	Black	Black	Red
Dilution	Black	Sepia	Cream
Red-eye	Red	Sepia	White
Albinism	Pink	White (sepia points)	White

It should be added that dilution of pigmentation may be produced by other factors than members of the albino series of allelomorphs. In the foregoing discussion such factors have been assumed to be absent. It may be said, however, that by starting with variations which owe their dilutions to factors which are independent of the albino series, doubly dilute varieties have been produced on introducing the dilution or red-eye allelomorphs of albinism. The effects of dilution, red-eye and albinism on brown pigment are parallel in all cases to their effects on black.

It should be said that the sepia (or "blue") due to the dilution factor, or to the red-eye factor, varies through a wide range which intergrades with black. Thus Castle (1905) and Sollas (1909) recognized that both intense and dilute forms of pigmentation occur commonly in guinea-pigs, but did not suggest any factorial explanation because of this intergrading. The inheritance of these fluctuations is at present under investigation.

If intensity, dilution, red-eye and albinism are allelomorphs, gametes should always carry one, but only one, of the four. Zygotes must always have two representatives from the series, never more or less, which two may, of course, be alike. Thus with dominance in the order of increasing pigmentation intense guinea-pigs should be homozygous, or else carry recessive dilution, recessive red-eye or recessive albinism, but never more than one of these; dilute guinea-pigs should be homozygous, or carry recessive red-eye or recessive albinism, but never both; red-eyes should be either homozygous or carry recessive albinism; and finally albinos should always be homozygous and never have the power of transmitting intensity, dilution, or red-eye to their descendants. All of these types have been obtained and tested with results in harmony with expectation. In this paper only a few of the most critical crosses will be given, reserving a more detailed discussion for a later paper.

Red-eye, as mentioned before, has occurred only in the descendants of certain pigs brought from Peru. No albinos appeared in the pure stock. In the pure races, red-eye behaved as a simple recessive. Thus intense by intense gave 63 intense and 19 red-eye young, while red-eye by red-eye gave only red-eyes, 28 in number.

As red-eyes had never appeared in our stock guinea-pigs, it was natural to expect that any stock pig crossed with red-eye, an apparently recessive condition, would give only intense young. As a matter of fact, however, numerous red-eye young appeared in F_1. The next question was whether one kind of stock differed from another in its power of bringing about this apparent reversal of dominance. A study of the records soon showed that albinism had something to do with the matter, as the following tabulation indicates:

	Intense	Red-eye	Albino
Red-eye × intense	48	22	20
Red-eye × albino	0	80	32

The difference in result of the two sorts of matings is obviously significant. With an intense parent there were more than 50 per cent. intense young and comparatively few red-eye young. With an albino parent there were no intense but numerous red-eye young. The intense animals and the albinos used were of the same stock and hence could differ consistently only as regards albinism. Clearly red-eye is not inherited independently of albinism. That the apparent reversal of dominance is not due merely to the presence of recessive albinism is shown by the fact that F_1 red-eyes crossed *inter se* produced 89 red-eyes, 36 albinos, but no intense young. Among these F_2 red-eyes, some were demonstrated to be free from recessive albinism. This complete inability of albinos to transmit the intense allelomorph of red-eye in crosses with the latter can only be interpreted in one way, aside from linkage hypotheses. The intense allelomorph of red-eye must also be an allelomorph of albinism. Thus red-eye must either be an allelomorph of albinism or be albinism itself, genetically, plus a modifying factor. The latter rather improbable hypothesis has been definitely eliminated. The pure South American stock under this hypothesis must be homozygous for all such modifying factors, since no albinos have appeared among them. The hypothetical modifying factor must be a dominant unit factor to account for the results given for F_1 and F_2.

Some pure South American intense animals were crossed with stock albinos. They produced F_1 intense young, which must (under the hypothesis) be heterozygous for albinism and for the modifying factor. These F_1 intense young were back-crossed with stock albinos. There should be both red-eyes and albinos among the young, 25 per cent. of each, if red-eye is albinism associated with a modifier. But no red-eyes actually appeared. There were 14 intense and 25 albinos. The chance that no red-eyes would appear in 39 young is $(3/4)^{39}$ or .000,001. Thus the hypothesis that red-eye is albinism plus a modifier may be dismissed.

On the view that red-eye is a dominant allelomorph of albinism, the results above are easily explained. Red-eye by albino or by red-eye should give only red-eyes and albinos. The F_1 intense, which must carry recessive albinism because of the stock albino parent, should not be able to transmit red-eye. As for hypotheses of linkage, it need only be said that no results have been obtained which require them. The critical crosses have all been made reciprocally as regards sex.

The fact that dilutes are more or less intermediate between intense and red-eye varieties suggested the following experiments which were designed to demonstrate at once whether there was any relation in inheritance between albinism and dilution. Dilutes were crossed with albinos from certain stocks which for years had given only intense and albino young, but no dilutes. Second, intense pigs from these same stocks, which had given only intense and albino young, were crossed with albinos from dilute stock. If intensity and dilution form a pair of allelomorphs which segregate independently of the pair, color and albinism (as is the case in mice and rabbits), these two crosses must give identical results. In each case color is introduced by one parent, albinism by the other; the intensity of certain stocks by one parent, the dilution of certain stocks by the other parent. In fact identical results should be obtained regardless of whether dilution is due to a unit factor or multiple factors, or even whether its inheritance is Mendelian or not, provided only that it is inherited independently of albinism. As it happened, these two crosses gave strikingly different results. The first cross, viz., dilute by albino from intense stock, gave only dilutes, 37 in number, aside from albinos. The second cross, intense from intense stock by albino from dilute stock, gave only intense young, 49 in number, aside from albinos. These different results can only be explained by assuming that a member of the albino series of allelomorphs, recessive to intensity, is essential to dilute animals. Thus genetically, dilution may be albinism plus a modifying factor, or it may be red-eye plus a modifying factor, or it may be a new allelomorph. The last has proved to be the case. A large number of intense animals, at least half of which under the first hypothesis would be expected to be heterozygous both for albinism and the modifying factor, have been crossed with albinos. None of them have given both albinos and dilutes. It is of course expected under the hypothesis of allelomorphism that no intense animal should transmit both albinism and dilution. The view that dilution is red-eye plus a modifying factor has also been eliminated. Red-eye has never appeared in our stock guinea-pigs, which must therefore be pure for any modifying factor which might change a red-eye to a dilute. But red-eyes of any generation crossed with stock albinos have never given dilutes in 105 young. Therefore dilution can not be red-eye plus a modifying factor. The only remaining hypothesis is that dilution is an allelomorph of red-eye and albinism. It is dominant to both since dilute by dilute has often given red-eyes and albinos, while the latter varieties crossed *inter se* have never given dilutes.

Thus we have four allelomorphs corresponding to four grades of pigmentation. The existence of such series has a bearing on the nature of unit factors. The results could be explained by perfect coupling, but such an explanation seems highly arbitrary where the characters fall into a natural physiological series. The series seems to suggest that we have four variations in some one entity. Furthermore, while we have only four such variations at the Bussey Institution, it may well be that others exist elsewhere, forming perhaps a continuous series. Such variations in this factor probably do not occur frequently. When they do occur they probably take place by distinct steps. The rather frequent occurrence of albinos in wild species, without intermediates, indicates that variation from one extreme to the other in the condition of the factor may take place.

A point which has a bearing on the physiology of pigment is the fact that members of the albino series of allelomorphs do not cause diminution in quantity of pigment, merely as pigment, but affect yellow pigment differently from black. This is seen most clearly in the red-eyes, in which yellow is completely inhibited, while black is only slightly affected.

Finally the question is raised whether anything similar to this can be found among other mammals. Albinos are found in many mammals as well as in lower animals. As to multiple allelomorphs, the case of the Himalayan rabbit is well known and compares well with the guinea-pig series. The Himalayan rabbit with its pink eyes and white fur with dark patches on nose, ears and feet is comparable to the guinea-pig albino. The complete albino rabbit recessive to the Himalayan is lower in the series than anything known in guinea-pigs. The dilution of the blue rabbit as well as that of the blue mouse and maltese cat is of a different type from the guinea-pig dilution. As Miss Sollas has shown, the pigment is clumped instead of uniformly decreased in quantity. The effect is slate-blue instead of sepia-brown. Mr. H. D. Fish has made crosses (unpublished data, to which I refer with his permission) which show as expected that rabbit dilution is inherited wholly independently of albinism.

In man, we have albinos which are probably comparable to guinea-pig and rabbit albinos. A study of the enormous collection of data in the Monograph of Pearson, Nettleship and Usher convinces one that albinism in man is recessive. But as Pearson points out, there are many grades of albinism and each grade tends to maintain its identity in inheritance. Among negroes there are albinos with blue irises, red pupils, white skin and nearly white hair. There are also darker grades, as with brown skin, eyes and hair. There is no sharp line anywhere between the complete albinos and the so-called xanthous types. In the white races albinos pass into the extreme blonds in a continuous series. In fact, study of records convinces one that in some cases the same factor may produce well-marked albinism, with red eyes, nystagmus and photophobia in one member of a family, but merely extreme blondism in another. It is worthy of note that human light hair resembles closely the sepia of dilute guinea-pigs, and not at all the slate blue of dilute rabbits, mice and cats. Thus, while I have not been able to find any critical evidence, the suggestion seems worth making that a series of allelomorphs of albinism may be in part responsible for differences in intensity of human pigmentation.

Summing up: the results in guinea-pigs and rabbits suggest that there is a hereditary factor in mammals, which may exist with stability at different stages of divergence from the normal; that divergence from the normal in the factor tends to produce in the animal a corresponding reduction in the quantity of melanin pigment throughout the body, conspicuously in fur, skin and eyes, of which reduction the limit is complete albinism; that in this reduction the qualitative differentiation of the pigment is a factor, in that yellow pigment is affected more strongly than black and its threshold of complete inhibition is reached with less divergence of the factor; that in the reduction the location of the pigment is a factor, in that there is less tendency toward reduction at the extremities—feet, ears and nose—than elsewhere in skin and fur; that, finally, any stage of divergence is dominant to any stage more remote from the normal.

In conclusion, I wish to thank Professor Castle for the opportunity to carry on this work and for numerous suggestions during its progress.

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